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Title: Benzimidazol-2-one derivatives useful for treating obstructive or inflammatory airway diseases

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Patent- og Varemærkestyrelsen
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PATENT- OG VAREMÆRKESTYRELSEN

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BENZIMIDAZOL-2-ONE DERIVATIVES USEFUL FOR TREATING OBSTRUCTIVE OR INFLAMMATORY AIRWAY DISEASES

TECHNICAL FIELD

This invention relates to novel benzimidazol-2-one derivatives useful for the treatment of obstructive or inflammatory airway diseases, in particular chronic obstructive pulmonary disease

BACKGROUND ART

EP 477819 describes benzimidazol derivatives acting on potassium (BK_{Ca}) channels, useful for the treatment of e g convulsions, asthma, hypertension and ischaemia The use of these compounds for treating obstructive or inflammatory airway diseases is neither teached nor suggested

EP 617023 describes benzimidazole derivatives useful as openers of potassium channels, and in particular for the treatment of hypertension, coronary artery spasms, asthma, ischemia, irritable bowl syndrome, spastic bladder, psychosis and convulsions The use of these compounds for treating obstructive or inflammatory airway diseases is neither teached nor suggested

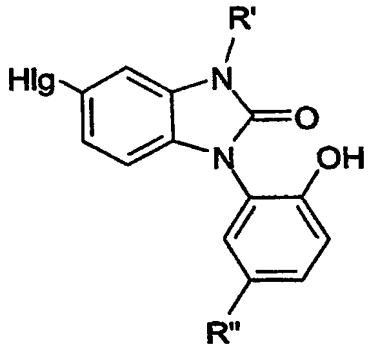
EP 747354 describes 3-substituted oxindole derivatives useful as maxi-K (BK_{Ca}) channel modulators The use of these compounds for treating obstructive or inflammatory airway diseases is neither teached nor suggested

Alyson et al [*Alyson JF, Barnes PJ, Venkatesan P and Belvisa MG* Activation of Large Conductance Potassium Channels Inhibits the Afferent and Efferent Function of Airway Sensory Nerves in the Guinea Pig, J Clin Invest 1997 **99** (3) 513-519] have shown that NS1619 (1,3-dihydro-1-[2-hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2H-Benzimidazol-2-one), an opener of large conductance calcium-activated potassium (BK_{Ca}) channels, inhibits the activity of myelinated and no-myelinated sensory fibers innervating the guinea pig airways via activation of BK_{Ca} channels, and suggest that selective BK_{Ca} channel openers could be of benefit in the treatment of airway disease by reducing both local and central airway reflexes resulting from the excitation and sensitisation of sensory fibers by mediators released during inflammatory conditions However this reference provides no indication of its usefulness in the treatment of obstructive or inflammatory airway diseases

SUMMARY OF THE INVENTION

According to the present invention it has now been found that a certain subgroup of benzimidazol-2-one derivatives are particularly well suited for use in the treatment of obstructive or inflammatory airway diseases Moreover these compounds have shown superior in respect of stability, bioavailability, and other properties relevant to drug candidates

Therefore, in its first aspect the invention provides a benzimidazol-2-one derivative of Formula I



(I)

wherein

R' represents hydrogen or alkyl,

R" represents halogen or trihalogenmethyl, and

Hlg represents halogen,

provided, however,

if Hlg is F, then R" is not Cl

In a second aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of the 1,5-disubstituted benzimidazol-2-one of the invention, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent, for the for the treatment, prevention or alleviation of an obstructive or inflammatory airway disease

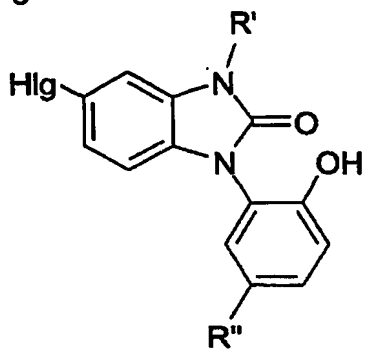
In a further aspect the invention provides method for the treatment, prevention or alleviation of obstructive or inflammatory airway diseases of a subject, including a human, which method comprises the step of administering to said subject in need thereof, a therapeutically effective amount of a benzimidazol-2-one derivative of the invention

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and the working examples

DETAILED DISCLOSURE OF THE INVENTION

Benzimidazol-2-one Derivative

In its first aspect the invention provides novel benzimidazol-2-one derivative represented by the following Formula I



(I)

wherein

R' represents hydrogen or alkyl,

R" represents halogen or trihalogenmethyl, and

Hlg represents halogen,

provided, however, if Hlg is F, then R" is not Cl

In a preferred embodiment Hlg represents Cl or Br

In another preferred embodiment R' represents hydrogen or methyl

In a further preferred embodiment R" represents halogen or CF_3 In a more preferred embodiment R" represents Cl or CF_3

In a most preferred embodiment the benzimidazol-2-one derivative of the invention is

1-(5-chloro-2-hydroxyphenyl)-5-chloro-1,3-dihydro-2H-benzimidazo-2-one, or

1-(5-trifluoromethyl-2-hydroxyphenyl)-5-chloro-1,3-dihydro-2H-benzimidazo-2-one,

or a pharmaceutically-acceptable salt thereof

Definition of Substituents

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom Thus, a trihalogenmethyl group designates e g a trifluoromethyl group, a trichloromethyl group or similar trihalogen-substituted methyl groups

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C_{1-18}-alkyl), more preferred of from one

to six carbon atoms (C_{1-6}-alkyl, lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl In another preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl

Pharmaceutically Acceptable Salts

The chemical substance for use according to the invention may be provided in any form suitable for the intended administration Suitable forms include pharmaceutically (i e physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulfate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like Such salts may be formed by procedures well known and described in the art

Metal salts of a compound for use according to the invention include alkali metal salts such as the sodium salt of a chemical compound of the invention containing a carboxy group

Steric Isomers

The chemical substance for use according to the invention may exist in (+) and (-) forms as well as in racemic forms (±) The racemates of these isomers and the individual isomers themselves are within the scope of the present invention

Racemic forms can be resolved into the optical antipodes by known methods and techniques One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix Racemic compounds of the present invention can thus be resolved into their optical antipodes, e g , by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example

The compound for use according to the invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like

Additional methods for the resolving the optical isomers are known in the art Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981)

Optical active compounds can also be prepared from optical active starting materials

Methods of Preparation

The compounds for use according to the invention may be prepared by conventional methods for chemical synthesis, e g those described in EP 477819, EP 617023 and EP 747354

Biological Activity

In another aspect the invention relates to the use of a chemical substance for the manufacture of a medicament for the treatment, prevention or alleviation of an obstructive or inflammatory airway disease

In a more preferred embodiment the obstructive or inflammatory airway disease is an airway hyperreactivity, a pneumoconiosis such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, a chronic obstructive pulmonary disease (COPD), bronchitis, excerbation of airways hyperreactivity or cystic fibrosis

In a most preferred embodiment the obstructive airway disease is chronic obstructive pulmonary disease (COPD)

Pharmaceutical Compositions

In another aspect the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a chemical substance as described herein, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent, for the treatment, prevention or alleviation of an obstructive or inflammatory airway disease

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a

pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries

In a preferred embodiment the invention provides pharmaceutical compositions comprising a chemical substance as described herein, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e g films or microcapsules

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray The compositions may be provided in single or multi-dose form

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas The aerosol may conveniently also contain a surfactant such as lecithin The dose of drug may be controlled by provision of a metered valve

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP) Conveniently the powder carrier will form a gel in the nasal cavity The powder composition may be presented in unit dose form for example in capsules or cartridges of, e g , gelatin, or blister packs from which the powder may be administered by means of an inhaler

In a preferred embodiment pharmaceutical composition of the invention is provided in the form of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less Such a particle size may be obtained by means known in the art, for example by micronization

When desired, compositions adapted to give sustained release of the active ingredient may be employed

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co , Easton, PA)

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner

The actual dosage depend on the nature and severity of the disease being treated and the route of administration, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect However, it is presently contemplated that pharmaceutical compositions containing of from about 0 01 to about 500 mg of active ingredient per individual dose, preferably of from about 0 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments

The active ingredient may be administered in one or several doses per day A satisfactory result can, in certain instances, be obtained at a dosage as low as 0 01 µg/kg i v and 0 1 µg/kg p o The upper limit of the dosage range is presently considered to be about 10 mg/kg i v and 100 mg/kg p o Preferred ranges are from about 0 1 µg/kg to about 10 mg/kg/day i v , and from about 1 µg/kg to about 100 mg/kg/day p o

Methods of Therapy

In another aspect the invention provides a method for the treatment, prevention or alleviation of an obstructive or inflammatory airway disease of a living animal body, including a human, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount of a chemical substance as described herein

In a preferred embodiment the obstructive or inflammatory airway disease is an airway hyperreactivity, a pneumoconiosis such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, a chronic

obstructive pulmonary disease (COPD), bronchitis, excerbation of airways hyperreactivity or cystic fibrosis

In its most preferred embodiment the obstructive airway disease is chronic obstructive pulmonary disease (COPD)

It is at present contemplated that a suitable dosage of the active pharmaceutical ingredient (API) is within the range of from about 0 1 to about 1000 mg API per day, more preferred of from about 10 to about 500 mg API per day, most preferred of from about 30 to about 100 mg API per day, dependent, however, upon the exact mode of administration, the form in which administered, the indication considered, the subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed

Example 1

Preparatory Example

N-(3-Chloro-6-methoxy-phenyl)-4-chloro-2-nitroaniline (Intermediate compound)

5-chloro-*O*-anisidine (4 1g, 26 mmol) in anhydrous *N,N*-dimethyl formamide (10 ml) was added sodium hydride (0 9 g 30 mmol) under a nitrogen atmosphere, and the reaction mixture was heat at 45°C for one hour Afterwards the mixture was cooled on and ice/water bath 2,5-Dichloro nitrobenzene (5 g, 26 mmol) was added and the reaction mixture was stirred at 85°C for 21 hours The reaction mixture was cooled and poured into water, and the precipitate was isolated by filtration The precipitate was dissolved in boiling ethyl alcohol (app 250 ml) and added charcoal The mixture was filtered, the filtrate was cooled, and the title compound precipitated and isolated by filtration

4-Chloro-N^1-(5-chloro-2-methoxy-phenyl)-benzene-1,2-diamine hydrochloride (Intermediate compound)

N-(3-Chloro-6-methoxy-phenyl)-4-chloro-2-nitroaniline (1 9 g, 6 1 mmol) in ethyl alcohol (50 ml) was added Raney nickel, and the reaction mixture was stirred under a nitrogen atmosphere and filtered through cecalite into hydrochloric acid (10 ml

of 1 M) in ethyl alcohol The filtrate was evaporated to dryness and diethyl ether was added The title compound was isolated by filtration

5-Chloro-1-(5-chloro-2-methoxy-phenyl)-1,3-dihydro-benzimidazol-2-one (Intermediate compound)

4-Chloro-N^1-(5-chloro-2-methoxy-phenyl)-benzene-1,2-diamine hydrochloride (6 3 g, 20 mmol) in tetrahydrofurane (70 ml) was added carbonyldiimidazole (9g 55 mmol) The reaction mixture was stirred at 60°C overnight, poured into water (app 200 ml) and extracted with ethylacetate, and the organic phase was washed with brine and evaporated to an oil The title compound was crystallized from toluene

5-Chloro-1-(5-chloro-2-hydroxy-phenyl)-1,3-dihydro-benzimidazole-2-one (Compound 1)

5-Chloro-1-(5-chloro-2-methoxy-phenyl)-1,3-dihydro-benzimidazol-2-one (4 g, 13 mmol) in dichloromethane was cooled to -10°C, and boron tribromide (14 6 ml 1 M solution in dichloromethane 14 6 mmol) was added The reaction mixture is stirred at room temperature for 6 hours, poured into water (app 200 ml), and stirred for 15 minutes and filtrated The title compound was crystallized from toluene/heptane M p 256-257°C

Example 2

Pharmacokinetic Parameters

In this example the pharmacokinetic parameters of Compound 1 of the invention are compared to those of a close analogue of the prior art, i e 1,3-dihydro-1-[2-hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2H-Benzimidazol-2-one (i e NS1619 described by *Alyson et al*, *Op cit*), herein designated the Reference Compound

Dosing of rats

Each compound was dosed to 6 male Wistar rats *i v* and the same for *p o* The rats were sampled as indicated in Table 1, below, but only 3 rats were sampled per time point The blood samples were centrifuged at 1 300 g at 4°C for 25 minutes and the resulting plasma samples were stored at < -15°C pending analysis

The compounds were dosed as clear solutions in phosphate buffer/Tween 80 (90 10) in a concentration of 3 mg/ml

Table 1

Dosing and sampling of rats

Compound	Dose *p o*	Dose *i v*	Sampling times *p.o.*	Sampling times *i.v*
Ref Cpd	30 mg/kg	3 mg/kg	0 min	0 min
			30 min	10 min
			1 h	30 min
			2 h	1 h
			3 h	2 h
			5 h	4 h
			8 h	7 h
			24 h	24 h
Cpd 1	30 mg/kg	3 mg/kg	0 min	0 min
			30 min	10 min
			1 h	30 min
			2 h	1 h
			3 h	2 h
			5 h	5 h
			8 h	7 h
			24 h	24 h

Sample preparation

Aliquots of samples, calibrants and QC's (100 µl) were pipetted into 1 5 ml eppendorf tubes To each tube (except matrix blank) was added 300 µl acetonitrile with internal standards Matrix blank was added 300 µl acetonitrile without internal standard

The tubes were shaken on a whirlimixer and then centrifuged for 25 minutes at 16 000g at 5°C to precipitate proteins

An aliquot (200 µl) of the supernatant was transferred to another 1 5 ml eppendorf tube and evaporated to dryness under a gentle stream of nitrogen at 40°C Then the samples were reconstituted in of mobile phase (initial composition)

Quality control samples and calibration standards

The results from quality control samples and calibration standards indicated a good quality of data

Table 2

Calibrations and QC's

Compound	Quality control samples ng/ml, n=3	Calibration standards ng/ml, n=1	Coefficient of determination	Weighting factor	Comments
Ref Cpd	2, 80, QCDx10 (1000), QCDx100 (10000)	0 5, 1, 3, 5, 10, 30, 80, 100, 300, 500 (ex)	0 9939	1/x	All QC's and calibrants except 500 ng/ml were within 15% deviation from nominal concentration
Cpd 1	QC_{low} 5ex, QC_{med} 80ex, QCDx10 (1000), QCDx100 (10000)	0 5, 1, 3, 5, 10, 30, 80, 100 ex, 300, 500, 800, 1000	0 9971	1/x	QC_{low} and QC_{med} was excluded, but the batch was accepted as 42 samples out of 48 were diluted

Ex Excluded due to deviation >15% to nominal concentration

QCD QC diluted

LC-MS/MS methods

Liquid chromatography

HPLC column Waters Xterra MS C8, 2 1 x 50 mm, 2 5 µm p s

Flow 200 µl/min

Mobile phase A 5 mM Ammonium acetate pH 6 7 (not pH adjusted)

Mobile phase B Acetonitrile

Injection volume 10 µl

Time between injections 10 min for Ref Cpd , 11 min for Cpd 1

Table 3

Elution Gradients

Gradient of Ref Cpd		Gradient of Cpd 1	
0 min	20% B	0 min	20% B
5 min	90% B	1 min	20% B
6 min	20% B	5 min	90% B
		6 min	90% B
		7 min	20% B

Mass spectrometry

MS instrument MicroMass Quattro II

Electrospray negative ion-mode

Source/desolvation temperature 110/330°C

Table 4

Multiple Reaction Mode (MRM) Settings

Compound	Capillary voltage	Cone voltage	Collision energy	Extractor	Transition
Ref Cpd	2	35	25	1	361 0→340 9
Cpd 1	3	25	21	3	293 0→249 9

Results

Incorporating the data from the rat plasma analyses, the pharmacokinetic parameters were calculated using WinNonLin Professional Edition version 2 0

Table 5

Pharmacokinetic data on Reference Compound and on Compound 1

Compound	*p.o* dose mg/kg	*i v* dose mg/kg	Bio-availability %	$T_{1/2}$ (*i v*) h (time-points)	$T_{1/2}$ (*p.o*) h (time-points)	T_{max} h *p.o*	C_{max} ng/ml *p.o*	V_d L/kg
Ref Cpd	30	3	145	1,7 h (5min-5h)	2,5 h (3-24h)	3 h	10000	1,1 L/kg
Cpd 1	30	3	97	0,8 h (5min-5h)	3,2 h (2-24 h)	0,5 h	4200	1,9 L/kg

Comments on the Results

As shown in Table 5 above, Compound 1 of the invention shows a faster absorption compared to the reference compound The C_{max} after *p o* administration is reached after only 30 minutes, compared to 3 hours for that of the reference compound This means that Compound has a faster onset of action

The half-life of both compounds after *p o* administration are comparable, although the half-life of Compound 1 seems to be slightly longer

Example 3

Stability in Solution

In this example the stability of Compound 1 of the invention are compared to those of a close analogue of the prior art, i e 1,3-dihydro-1-[2-hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2H-Benzimidazol-2-one (i e NS1619 described by *Alyson et al*, *Op cit*), herein designated the Reference Compound

The stability is determined in neutral (H_2O), in basic (0 1M NaOH) and in acidic solution (0 1M HCl)

Experimental Conditions for the Reference Compound

Stability in water

50 ml of water was added to 27 mg of the reference compound The compound was only partly dissolved The suspension was stored at 60°C and after 24 hours 25 ml of methanol was added in order to completely dissolve reference compound The solution was stored for further 4 hours and then analysed by HPLC (t = 28 hours)

Stability in 0 1M HCl

50 ml of 0 1M hydrochloric acid was added to 27 mg of the reference compound The compound was only partly dissolved The suspension was stored at 60°C and after 48 hours 25 ml of methanol was added in order to completely dissolve the reference compound The solution was stored for further 4 hours and then analysed by HPLC (t = 52 hours)

Stability in 0.1M NaOH

50 ml of 0 1M sodium hydroxide was added to 24 mg of the reference compound The compound was completely dissolved The solution was stored at 60°C and analysed by HPLC after 2 hours (t = 2 hours)

Experimental Conditions for Compound 1

Stability in water

50 ml of water was added to 25 mg of Compound 1 The compound was only partly dissolved The suspension was stored at 60°C, and after 48 hours, 25 ml of acetonitrile was added in order to completely dissolve Compound 1 The solution was stored for further 24 hours and then analysed by HPLC (t = 72 hours)

Stability in 0 1M HCl

50 ml of 0 1M hydrochloric acid was added to 27 mg of Compound 1 The compound was only partly dissolved The suspension was stored at 60°C, and after 48 hours, 25 ml of acetonitrile was added in order to completely dissolve Compound 1 The solution was stored for further 24 hours and then analysed by HPLC (t = 72 hours)

Stability in 0 1M NaOH

50 ml of 0 1M sodium hydroxide was added to 26 mg of Compound 1 The compound was completely dissolved The solution was stored at 60°C and analysed by HPLC after 72 hours (t = 72 hours)

The results of the stability determinations are presented in Table 6 below

Table 6

Stability of Compound 1 and Reference Compound

Area% (UV 225 nm) of the Test Substance

	Reference Compound	**Compound 1**
Water, 60°C	Initial 98 4%	Initial 99 7%
	t = 28 hours 96 7%	t = 72 hours 99 6%
HCl, 60°C	Initial 98 4%	Initial 99 7%
	t = 52 hours 98 4%	t = 72 hours 99 6%
NaOH, 60°C	Initial 98 4%	Initial 99 7%
	t = 2 hours 0 0%	t = 72 hours 99 4%

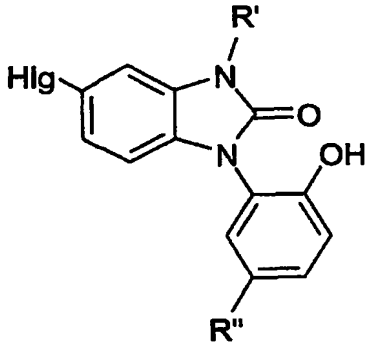
The compound of the invention is stable at all conditions

The reference compound is unstable in neutral to basic solutions It degrades instantly when dissolved in 0 1 M NaOH, and the compound degraded after 2 hours of storage at 60°C

5

CLAIMS

1 A 1,5-disubstituted benzimidazol-2-one derivative having the general Formula I



(I)

wherein
R' represents hydrogen or alkyl,
R" represents halogen or trihalogenmethyl, and
Hlg represents halogen,
provided, however,
if Hlg is F, then R" is not Cl

2 The benzimidazol-2-one derivative of claim 1, wherein
Hlg represents Cl or Br

3 The benzimidazol-2-one derivative of either of claims 1-2, wherein
R' represents hydrogen or methyl

4 The benzimidazol-2-one derivative of any of claims 1-3, wherein
R" represents halogen or CF_3

5 The benzimidazol-2-one derivative of claim 4, wherein
R" represents Cl or CF_3

6 The benzimidazol-2-one derivative of any of claims 1-5, which is
1-(5-chloro-2-hydroxyphenyl)-5-chloro-1,3-dihydro-2H-benzimidazo-2-one, or
1-(5-trifluoromethyl-2-hydroxyphenyl)-5-chloro-1,3-dihydro-2H-benzimidazo-2-one,
or a pharmaceutically-acceptable salt thereof

7 A pharmaceutical composition comprising a therapeutically effective amount of the 1,5-disubstituted benzimidazol-2-one derivative of claims 1-6, or a

pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent, for the for the treatment, prevention or alleviation of an obstructive or inflammatory airway disease

8 The pharmaceutical composition of claim 7, provided in the form of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant

9 The use of a benzimidazol-2-one derivative according to any of claims 1-6 for the manufacture of a medicament for the treatment, prevention or alleviation of an obstructive or inflammatory airway disease

10 The use according to claim 9, wherein the obstructive or inflammatory airway disease is an airway hyperreactivity, a pneumoconiosis such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, a chronic obstructive pulmonary disease (COPD), bronchitis, excerbation of airways hyperreactivity or cystic fibrosis

11 The use according to claim 9, wherein the obstructive airway disease is chronic obstructive pulmonary disease (COPD)

12 A method of treatment, prevention or alleviation of an obstructive or inflammatory airway disease of a living animal body, including a human, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount of a benzimidazol-2-one derivative according to any of claims 1-6, or a pharmaceutically-acceptable salt thereof

13 The method according to claim 12, wherein the obstructive or inflammatory airway disease is an airway hyperreactivity, a pneumoconiosis such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, a chronic obstructive pulmonary disease (COPD), bronchitis, excerbation of airways hyperreactivity or cystic fibrosis

14 The method according to claim 12, wherein the obstructive airway disease is chronic obstructive pulmonary disease (COPD)

ABSTRACT

BENZIMIDAZOL-2-ONE DERIVATIVES USEFUL FOR TREATING OBSTRUCTIVE OR INFLAMMATORY AIRWAY DISEASES

This invention relates to novel benzimidazol-2-one derivatives useful for the treatment of obstructive or inflammatory airway diseases, in particular chronic obstructive pulmonary disease